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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/438,358	11/12/99	GERARD	G	0942.4640001

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EXAMINER	
LEFFERS JR,G	
ART UNIT	**PAPER NUMBER**
1636	08

DATE MAILED: 11/08/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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1- File Copy

G.P.O. 2000 ; 465-188/25266

Office Action Summary

Application No.	Applicant(s)
09/438,358	Gerard, et al.
Examiner	**Group Art Unit**
Gerald G. Leffers Jr.	1636

☒ Responsive to communication(s) filed on *Aug 21, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-64* is/are pending in the application.

Of the above, claim(s) *1-13 and 52-64* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *14-51* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-13 and 52-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6. Upon further review of the claims and specification, the election of species requirements made in the Restriction Requirement have been withdrawn.

Acknowledgment is also made of applicants' IDS filed 9/18/00. However, none of the listed references were located with the file. Examiner has located several of the references with a prior application and these references have been considered. The signed and initialed PTO 1449 for these references has been mailed along with this application.

Specification

Claims 14-51 are objected to because of the following informalities: each of the claims encompass in vivo embodiments whereas applicant has elected only in vitro embodiments. It would be remedial to amend the claim language to clearly indicate that the claimed methods are in vitro methods for recombinational cloning. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 19 are vague and indefinite in that the metes and bounds of the term "effective amount" of a ribosomal protein are unclear. How much of a ribosomal protein constitutes an effective amount when it is added to a recombination reaction? It would be remedial to amend the claim language to clearly indicate what constitutes an "effective amount" of a ribosomal protein when it comes to recombination of nucleic acids.

Claims 14 and 19 are also vague and indefinite in that the metes and bounds of the term "do not substantially recombine" are unclear. The term does not appear to be well defined in the specification and is inherently indefinite. Would a single instance of recombination constitute "substantial" recombination? Would 5 instances of recombination between the two sites constitute "substantial recombination"? Exactly what frequency of recombination between the sites would constitute "substantial" recombination? It would be remedial to amend the claim language to clearly indicate what is intended by the limitation of no "substantial recombination".

Claim 19 is vague and indefinite in that the metes and bounds of the phrase "..two or more different Vector Donor molecules comprising two or more recombination sites.." are unclear. Read one way the phrase implies that between the two or more different vector donor molecules there is a sum of at least two recombination sites. From reading the specification,

however, it appears the phrase is meant to specify that each of the Vector Donors has at least two recombination sites. It would be remedial to amend the claim language to clearly indicate that each of the Vector Donor molecules has two recombination sites.

Claim 31 is vague and indefinite in that it is dependent upon a nonelected claim. It would be remedial to amend the claim language to incorporate the limitations of claim 1, upon which claim 31 is dependent.

Claims 32-33 are vague and indefinite in that the metes and bounds of the term "derived from" are unclear. The nature and number of steps required to make a "derivative" of a given nucleic acid are inherently unclear and the term implies steps which may alter the basic characteristics of the starting material. It would be remedial to amend the claim language by using the term "obtained from" which implies a more direct process for obtaining the desired nucleic acid for use in the claimed method.

Claims 37-38 are vague and indefinite in that it is not clear from reading the specification what the difference is between vector "propagation" and vector "replication" in a host cell. It would be remedial to simply use one of the terms in the claim language.

Claim 37 is also vague and indefinite in that the use of the phrase "and/or insect cells" after a listing of other cell types makes it unclear which other cell type in addition to the mammalian cells, which immediately precede the phrase, are to be included with insect cells. It would be remedial to amend the claim to more clearly indicate which combinations of host cell types are to be encompassed for the claimed eukaryotic vector.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: incubation of more than one nucleic acid comprising at least one site-specific recombination site to form a product nucleic acid.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 31-32, 36, 38-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Nash (Methods in Enzymology. Vol. 100, pp 210-216, see the entire reference).

Nash teaches the purification of the lambda Integrase (Int) protein and characterization of its activity throughout the purification process (Abstract; Table on page 214). The assay utilized to measure Integrase activity featured a linearized DNA bearing one Int recognition sequence and a supercoiled plasmid bearing a second Int recognition sequence (page 211, second paragraph - page 212, second paragraph). Recombination of the two DNA molecules produced a linear DNA

having the "desirable" properties of being larger and possessing Int recognition sites attL and attR. Since Int was purified from E.coli cells after overexpression of Int from a plasmid bearing the Int gene, it is inherent that the crude extracts used for the in vitro assay would include the E.coli ribosomal proteins, integration host factor (IHF), HU and the Int recombinase. Nash also teaches the addition of crude preparations of IHF to in vitro recombination mixtures to enhance recombination (page 215, second full paragraph).

Claims 40-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Abremski et al (V)(The Journal of Biological Chemistry, Vol. 259, No. 3, pages 1509-1514; see entire document) and Abremski et al (W)(The Journal of Biological Chemistry. Vol. 257, No. 16, pages 9658-9662; see entire document).

The references teach the purification and characterization of the site-specific recombination enzymes Cre and Xis, respectively. Both references utilize a single recombinant vector comprising two recombinations sites in an in vitro assay in which the products of recombination are two smaller, circular DNAs which can be cut with a single restriction enzyme and run on an agarose gel to assay formation of the different recombination products. In both instances, the enzymes were prepared from crude extracts of E.coli cells in which the enzymes were overexpressed and the enzymatic activity followed throughout the purification process (Table I of both papers). It is reasonable to expect that the E.coli ribosomal proteins as well has the E.coli proteins IHF and HU would have been present in each of the crude extracts tested.

Claims 14-51 are rejected under 35 U.S.C. 102(e) as being anticipated by Hartley et al (A)(U.S. Patent No. 5,888,732; see the entire document).

Hartley et al teach recombinational cloning methods which can be practiced in vivo and in vitro (Abstract; Figure 1). The methods can be practiced with each of the recombination factors specified in the rejected claims (e.g. Cre, Int, etc). In vitro applications would be expected to encompass embodiments wherein the methods are practiced with crude E.coli lysates comprising one or more recombination factors (e.g. IHF, HU and a recombinantly expressed recombinase) and wherein one or more E.coli ribosomal proteins would be present.

Because it could be considered that in vitro embodiments of the methods taught by Hartley et al comprising the use of a crude extract from E.coli having one or more recombination factors and ribosomal proteins for recombinational cloning is not encompassed by the teachings of the '732 patent, a rejection of the claims under 35 U.S.C. 103(a) follows.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-51 rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al (A) in view of Nash (U) or Abremski et al (V) or Abremski et al (W).

Hartley et al teach recombinational cloning methods which can be practiced in vitro and in vivo and which encompass each of the limitations of the instant claims (e.g. types of recombinases, DNA molecules used as substrates, Insert Donors, Vector Donors, etc.)(Abstract; Figure 1; see the entire document).

Hartley et al do not explicitly teach the use of crude lysates comprising recombination factors in their in vitro methods. Hartley et al do not explicitly teach the addition of ribosomal proteins to their recombination reaction mixtures.

The teachings of Nash, Abremski et al (V) and Abremski et al (W) are described above with regard to the use of crude lysates comprising the recombination proteins Int, Xis, IHF and Cre in vitro recombination reactions.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use crude E.coli lysates comprising one or more recombination proteins in the methods

taught by Hartley et al for recombinational cloning because Hartley et al teach that their methods can be practiced in vitro and because Nash and the Abremski et al references teach that one can supply recombination proteins with crude extracts of E.coli cells comprising one or more recombination proteins for in vitro recombination reactions which effectively produce different recombination products. One would have been motivated to do so in order to receive the expected benefit of providing one or more recombination proteins without the need for further purification and, in the case of Int/Xis, providing multiple factors known to enhance recombination. Such extracts would be expected to also comprise the ribosomal proteins expressed in E.coli. Based on the entirety of the combined teachings above, and absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing a crude extract comprising one or more recombination proteins to practice the recombinational cloning methods taught by Hartley et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-51 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-37 of U.S. Patent No. 5,888,732. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reason.

The instant claims are drawn to in vitro methods of recombinational cloning wherein ribosomal proteins are also included in the recombination reaction mixture. The cited claims from the '732 patent are all directed to in vitro methods of recombinational cloning which would encompass the use of crude cell extracts from E.coli to provide one or more recombination proteins to the in vitro recombination reaction mixture. Such crude cell extracts would be expected to comprise one or more of the E.coli ribosomal proteins. Thus, the claims of the instant application are entirely encompassed by the claims of the '732 patent and are merely obvious variants of the claimed invention from the '732 patent.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R.

§ 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GLJ

G. Leffers, Jr.

Patent Examiner

Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER

November 5, 2000